DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 8, 2002

Zach W. Hall, Ph.D.
Executive Vice Chancellor
University of California, San Francisco
513 Parnassus Avenue, Room S-101
San Francisco, California 94143-0407

RE: Human Research Subject Protections Under Federal Wide Assurance (FWA) FWA-00000068 and Multiple Project Assurance (MPA) M-1169

Research Project: Prospective, Randomized, Muticenter Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation and Lisofylline vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

Principal Investigator: Michael A. Matthay, M.D.

UCSF Approval Number: H2811-12480-04A

Research Publication: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (N. Engl J Med 2000;342:1301-8)

HHS Project Number: N01-HR46063

Dear Dr. Hall:

The Office for Human Research Protections (OHRP) has reviewed the University of California at San Francisco's (UCSF's) December 14, 2000 report that was submitted in response to OHRP's August 3, 2000 letter to UCSF regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced

research:

(1) HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere under the HHS regulations, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 102(c) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(a) UCSF's report indicated the following:

(i) 36 of the 43 subjects enrolled in the study protocol at San Francisco General Hospital were unable to provide legally effective informed consent, and consent for these subjects instead was obtained and documented from another individual (spouse, adult child, parent, adult sibling).

(ii) 53 of the 62 subjects enrolled in the study protocol at UCSF Medical Center were unable to provide legally effective informed consent, and consent for these subjects instead was obtained and documented from another individual (spouse, adult child, parent, adult sibling, surrogate or surrogate with a designated Power of Attorney).

(b) UCSF's report stated the following regarding a description of the applicable state and local laws that established an individual who consented on the behalf of a subject enrolled in the research as the legally authorized representative of such subject.

"The use of relatives as representatives able to provide consent is in accord with medical and research practice in California and has been approved in the past by UCSF Legal Counsel."

(c) UCSF's report stated that at the UCSF Medical Center site, informed consent was obtained for subject 0910046 from an individual with legal power of attorney. Please clarify in detail (i) who this individual was; and (ii) whether the power of attorney was applicable to health care decisions and to surrogate consent for participation in research procedures.

(d) UCSF's report stated that at the UCSF Medical Center site, informed consent was obtained for subjects 0913061, 0913062 and 0913063 from "surrogates." Please clarify in detail (i) who these surrogates were; and (ii) the legal basis for these individuals having been designated as the legally authorized representatives for these subjects.

(e) Please provide OHRP with copies of all relevant local and state laws related to surrogate consent procedures and next-of-kin decision making for health care delivery that were in effect when the research was conducted. Please clarify the basis for the UCSF legal counsel's approval of the use of relatives to provide consent and whether this approval extends to surrogates.

(2) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of Institutional Review Board (IRB) meetings be in sufficient detail to show, among other things, the vote on these actions, including the number of members voting for, against, and abstaining. OHRP finds that minutes of UCSF IRB meetings provided with UCSF's report failed to satisfy this requirement.

(3) OHRP finds that the informed consent documents reviewed and approved by the UCSF IRB failed to adequately describe the reasonably foreseeable risks and discomforts of the research, in accordance with the requirements of HHS regulations at 45 CFR 46.116(a)(2). In specific, OHRP finds that the informed consent documents failed to describe the following risks and potential discomforts associated with the non-traditional, 6 ml/kg tidal volume group that were described in the UCSF IRB-approved protocol: dyspnea, agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia.

(4) OHRP finds that the UCSF IRB approved informed consent document failed to include an explanation of whom to contact for answers to pertinent questions about the research subjects' rights as required by HHS regulations at 45 CFR 46.116(a)(7).

(5) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by use of a *written* consent form approved by the IRB and that is signed by the subject or the subject's legally authorized representative, unless the IRB waives this requirement in accordance with 45 CFR 46.117(c). An IRB may waive the requirement for the investigator to obtain a signed consent in accordance with 45 CFR 46.117(c) if it finds either that (a) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality, or (b) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is

normally required outside of the research context.

(a) UCSF's report stated: "The investigators have told us that for approximately 13% of the subjects at the UCSF sites consent was obtained from a representative during the course of a witnessed telephone call. Use of telephone calls to obtain consent was not approved by the IRB, and copies of the consent form were not provided to the representatives prior to consent." OHRP finds that witnessed telephone consent by the subject's legally authorized representative failed to comply with the requirements for waiver of documentation of informed consent as required by 45 CFR 46.117(c). Furthermore, OHRP finds that the investigator initiated a change in the research without approval of the UCSF IRB in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4)(iii).

(b) UCSF's report stated that at the San Francisco General Hospital site, 4 subjects who "either could not hold a pen or focus on the form to consent," gave consent by a nodding gesture that was documented and witnessed by a registered nurse. OHRP finds that informed consent was not documented by a written consent form signed by the subjects for this research.

Required Action: OHRP acknowledges that the research has been completed. By March 15, 2002, UCSF must submit to OHRP a detailed corrective action plan to address findings (2), (3) (4) and (5) above for any ongoing or planned research activities.

(6) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four criteria when waiving the requirements to obtain informed consent. OHRP finds no evidence in the IRB records that the UCSF IRB made and documented these four criteria when it approved the principal investigator's February 3, 1999 request for a waiver of the requirement to obtain informed consent for collection of data from the medical records of patients who were screened for participation but were not enrolled.

Required Action: OHRP notes UCSF's report acknowledging that the approval of the above waiver of the requirement to obtain informed consent was made in error. By March 15, 2002, UCSF must submit to OHRP a satisfactory corrective action plan to ensure that the UCSF IRB makes and documents the four criteria required by HHS regulations at 45 CFR 46.116(d) whenever the UCSF IRB (i) approves a consent procedure which does not include, or which alters, some or all of the required elements of informed consent; or (ii) waives the requirements to obtain informed consent.

Recommended Action: Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(7) OHRP notes that the last sentence in the second paragraph in section 4.6 Subject Recruitment of the subject protocol states: "Because the study will include non-English speaking subjects, translators will be used." UCSF's report states that interpreters were used in the consent process involving several representatives of enrolled subjects. UCSF's report states also that UCSF is "working to establish new guidance that will balance potential participants' right to share in the potential benefits of research participation with the need to provide potential participants with consent documents in their own language."

Recommended action: HHS regulations require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (see 45 CFR 46.116 and 46.117). OHRP advises that where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language understandable to them. OHRP strongly encourages the use of this procedure whenever possible.

Alternatively, HHS regulations at 45 CFR 46.117(b)(2) permit oral presentation of informed consent information in conjunction with a short form written informed consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written informed consent document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

Based upon its review, OHRP has the following additional questions and concerns regarding the above-referenced research:

(8) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with, among other things, a description of the procedures to be followed, and identification of any procedures which are experimental.

OHRP notes the following statement in the above-referenced publication (N. England J Med 2000;342:1301-8):

> "Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight."

OHRP is concerned that the UCSF IRB-approved informed consent document failed to describe the 12 ml/kg tidal volume as being the traditional volume used for ventilatory support and the 6 ml/kg as being experimental or non-traditional. Furthermore, OHRP is concerned that the following statements in the UCSF IRB-approved informed consent document were misleading because it implied that both tidal volumes were used with equal frequency in clinical practice at UCSF:

> "Presently, doctors use varying volumes of oxygen-enriched air to inflate the lungs. It is unknown whether it is better to use a large or small volume of oxygen-enriched air to inflate the lungs of patients with lung injury.
>
> "Both ways of using the breathing machine are acceptable methods that are commonly used in medical practice."

Please respond. In your response, please clarify (a) the relative frequency with which 12 ml/kg and 6 ml/kg tidal volumes were used in clinical practice at UCSF at the time the research was initially reviewed by the UCSF IRB; (b) whether the UCSF IRB was aware of these statistics when it initially approved the research; and (c) which members of the UCSF IRB who participated in the initial and continuing review of the protocol had expertise in critical care medicine and ventilatory support.

(9) HHS regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the IRB shall determine that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of the subjects. OHRP is concerned that (a) both the subjects of the research, because

of their impaired mental state, and the subjects' family members, because of the psychological stress of having a critically ill family member being treated in an intensive care unit, appear to have likely been vulnerable to coercion or undue influence; and (b) the UCSF IRB failed ensure that there were additional safeguards included in the study to protect the rights and welfare of these vulnerable subjects. In particular, OHRP notes a lack of important details regarding the recruitment and enrollment of subjects, and finds no evidence in the UCSF IRB-approved protocol or other relevant UCSF IRB records that additional safeguards were included during the subject recruitment and enrollment process. Please respond in detail.

Please submit UCSF's response to the above questions and concerns so that OHRP receives it no later than March 15, 2002. If upon further review of the questions and concerns UCSF identifies additional instances of noncompliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: W. Sue Shafer, Ph.D., Assistant Vice Chancellor, Office of Research Administration, UCSF
Dr. Reese T. Jones, IRB Chair, Committee A, UCSF
Dr. Susan Sniderman, IRB Chair, Committee 1, UCSF
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
Commissioner, FDA
Dr. David A. Lepay, FDA

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